First Onset and Duration of Treatment-Emergent Adverse Events in Patients With Major Depressive Disorder Treated With Adjunctive Lumateperone 42 mg: A Pooled Analysis of 2 Randomized Placebo-Controlled Trials

Willie R. Earley, MD[1]; Suresh Durgam, MD[1]; Susan G. Kozauer, MD[2]; Changzheng Chen, PhD[1]; Andrew J. Cutler, MD[3]; Stephen M. Stahl, MD, PhD[4]

[1] Intra-Cellular Therapies, a Johnson & Johnson company, Bedminster, NJ, USA; [2] Former employee of Intra-Cellular Therapies, a Johnson & Johnson company, Bedminster, NJ, USA; [3] Department of Psychiatry, SUNY Upstate Medical University, Lakewood Ranch, FL, USA; [4] Department of Psychiatry, University of California, San Diego and Riverside; La Jolla, CA, USA

Background

- Major depressive disorder (MDD) is a common mental illness that negatively impacts quality of life, work productivity, and cognitive functioning[1,2]
- Standard antidepressant therapy (ADT), such as selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors, are used to treat MDD but can be limited by tolerability concerns[3]
  - Adverse effects associated with ADTs (eg, sexual dysfunction, weight gain, and sleep disturbances) may reduce treatment adherence[3]
- Given the limited efficacy and tolerability of standard ADTs, alternative strategies are used, including adjunctive antipsychotic treatment, which has shown efficacy in patients with MDD[4,5]
- Lumateperone is a mechanistically novel US Food and Drug Administration–approved antipsychotic to treat adults with schizophrenia and depressive episodes associated with bipolar I or bipolar II disorder as monotherapy and as adjunctive therapy with lithium or valproate, and as adjunctive therapy with ADT for MDD[6]
  - Lumateperone is a simultaneous modulator of serotonin, dopamine, and glutamate neurotransmission[7]
  - Specifically, lumateperone is a potent serotonin 5-HT_{2A} receptor antagonist, a dopamine D_2 receptor presynaptic partial agonist and postsynaptic antagonist, a D_1 receptor-dependent indirect modulator of glutamatergic AMPA and NMDA currents, and a serotonin reuptake inhibitor[7]
  - This novel mechanism of action with multimodal effects may confer robust efficacy with improved tolerability compared with current treatment options
- The efficacy and safety of lumateperone 42 mg adjunctive to ADT were demonstrated in two Phase 3, double-blind, placebo-controlled studies (Study 501 [NCT04985942]; Study 502 [NCT05061706]) in patients with MDD with inadequate ADT response[8,9]
  - The primary and key secondary efficacy endpoints were met in both trials, with lumateperone 42 mg + ADT significantly improving Montgomery-Åsberg Depression Rating Scale (MADRS) Total score and Clinical Global Impression–Severity (CGI-S) score, respectively, from baseline to Day 43 compared with placebo + ADT[8,9]
  - Additionally, lumateperone + ADT was generally safe and well tolerated, with minimal to low risk of extrapyramidal symptoms, weight gain, prolactin increase, or cardiometabolic effects[8,9]
- This pooled analysis of Study 501 and Study 502 assessed the first onset and duration of treatment-emergent adverse events (TEAEs) with lumateperone 42 mg + ADT in patients with MDD with an inadequate response to ADT

Methods

- Safety and tolerability data were pooled from Study 501 and Study 502 for the lumateperone 42 mg + ADT group and for the placebo + ADT group[8,9]
  - Both studies evaluated 6-week oral lumateperone 42 mg + ADT or placebo + ADT
  - Eligible males and females (aged 18-65 years) met DSM-5 criteria for MDD with inadequate response to 1 to 2 courses of ADT in the current depressive episode, were experiencing a major depressive episode (MADRS Total score ≥24 and CGI-S score ≥4), and had Quick Inventory of Depressive Symptomatology-Self Report-16 item score ≥14 at screening and baseline
  - Inadequate response to ADT was defined as <50% improvement with ≥6 weeks ADT monotherapy, as confirmed by the Antidepressant Treatment Response Questionnaire
- Safety assessments included AEs, time to first TEAE onset, and TEAE duration, analyzed descriptively

Results

Patient Population

- Of 964 patients treated in the pooled safety population (lumateperone + ADT, n=483; placebo + ADT, n=481), 91.4% completed treatment
- Demographics and baseline characteristics were similar between groups (**Table 1**)
  - The patient population was predominantly female and White

Table 1. Baseline Demographics and Clinical Characteristics (Safety Population)

	Lumateperone 42 mg + ADT (n=483)	Placebo + ADT (n=481)
Age, mean (range), years	45.3 (18-65)	45.8 (18-65)
Sex, n (%)		
Female	327 (67.7)	325 (67.6)
Male	156 (32.3)	156 (32.4)
Race, n (%)		
White	415 (85.9)	414 (86.1)
Asian	41 (8.5)	36 (7.5)
Black	26 (5.4)	24 (5.0)
Other[a]	1 (0.2)	7 (1.5)
Hispanic or Latino ethnicity, n (%)	51 (10.6)	49 (10.2)
No. of ADT failures in current episode based on ATRQ, n (%)		
1	434 (89.9)	420 (87.3)
2	49 (10.1)	61 (12.7)
ADT during double-blind treatment, n (%)		
SSRI	328 (67.9)	312 (64.9)
SNRI	126 (26.1)	138 (28.7)
Other (bupropion)	29 (6.0)	31 (6.4)

[a]Other includes Native Hawaiian or other Pacific Islander, multiple, or other.
ADT, antidepressant therapy; ATRQ, Antidepressant Treatment Response Questionnaire; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Adverse events

- TEAEs occurred in 68.1% of patients in the lumateperone + ADT group, compared with 45.1% in the placebo + ADT group (**Table 2**)
  - In the lumateperone + ADT group, dizziness, dry mouth, somnolence, nausea, fatigue, and diarrhea were reported in ≥5% of patients and at more than twice the rate of placebo + ADT
  - Serious TEAEs occurred in 1 patient per group and were unrelated to treatment (lumateperone + ADT, polypectomy; placebo + ADT, joint dislocation)
  - No patients died during the treatment period

Table 2. Summary of Adverse Events (Safety Population)

	Lumateperone 42 mg + ADT (n=483) n (%)	Placebo + ADT (n=481) n (%)
≥1 TEAE	329 (68.1)	217 (45.1)
Drug-related TEAE	244 (50.5)	97 (20.2)
SAE[a]	1 (0.2)	1 (0.2)
Drug-related SAE	0	0
Leading to treatment discontinuation		
AE	42 (8.7)	4 (0.8)
Drug-related AE	39 (8.1)	4 (0.8)
SAE	0	0
Death	0	0
TEAEs in lumateperone + ADT group at ≥5% and at least twice placebo + ADT		
Dizziness	79 (16.4)	24 (5.0)
Dry mouth	61 (12.6)	16 (3.3)
Somnolence	49 (10.1)	10 (2.1)
Nausea	41 (8.5)	19 (4.0)
Fatigue	35 (7.2)	6 (1.2)
Diarrhea[b]	22 (4.6)	6 (1.2)

[a]SAEs during treatment were 1 of each polypectomy (lumateperone + ADT group) and joint dislocation (placebo + ADT group); these SAEs were unrelated to study drug. [b]Included due to rounding up to 5%.
ADT, antidepressant therapy; AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

- In both the lumateperone + ADT and placebo + ADT groups, most patients had TEAE onset within the first week of study drug administration (**Table 3**)
  - Greater proportions of patients in the lumateperone + ADT group (45.3%) had TEAEs in the first week of the double-blind treatment period compared with patients in the placebo + ADT group (17.7%)
  - In the lumateperone + ADT group, rates of first TEAE onset steadily decreased over time after Week 1
  - The rates among patients in the placebo + ADT group decreased after Week 1 through Week 5 and increased after Week 5
- First onset of the most common TEAEs (dizziness, dry mouth, somnolence, nausea, fatigue, and diarrhea) decreased to <2% in Week 2 and <1% in Week 4 in both treatment groups (**Table 3**)

Table 3. First Onset of Common[a] TEAEs During Treatment (Safety Population)

Patients with first TEAE onset, n (%)[b]	Lumateperone 42 mg + ADT (n=483)						Placebo + ADT (n=481)					
	≤1 Week (N1=483)	>1 and ≤2 Weeks (N1=465)	>2 and ≤3 Weeks (N1=450)	>3 and ≤4 Weeks (N1=437)	>4 and ≤5 Weeks (N1=432)	>5 Weeks (N1=429)	≤1 Week (N1=481)	>1 and ≤2 Weeks (N1=480)	>2 and ≤3 Weeks (N1=476)	>3 and ≤4 Weeks (N1=472)	>4 and ≤5 Weeks (N1=466)	>5 Weeks (N1=461)
≥1 TEAE	219 (45.3)	39 (8.4)	32 (7.1)	18 (4.1)	12 (2.8)	9 (2.1)	85 (17.7)	30 (6.3)	30 (6.3)	25 (5.3)	17 (3.6)	30 (6.5)
Dizziness	57 (11.8)	9 (1.9)	5 (1.1)	3 (0.7)	2 (0.5)	3 (0.7)	13 (2.7)	2 (0.4)	5 (1.1)	0	0	4 (0.9)
Dry mouth	40 (8.3)	7 (1.5)	7 (1.6)	3 (0.7)	2 (0.5)	2 (0.5)	6 (1.2)	1 (0.2)	3 (0.6)	2 (0.4)	2 (0.4)	2 (0.4)
Somnolence	41 (8.5)	5 (1.1)	0	1 (0.2)	0	2 (0.5)	7 (1.5)	1 (0.2)	1 (0.2)	0	0	1 (0.2)
Nausea	29 (6.0)	6 (1.3)	3 (0.7)	1 (0.2)	1 (0.2)	1 (0.2)	12 (2.5)	0	1 (0.2)	3 (0.6)	2 (0.4)	1 (0.2)
Fatigue	25 (5.2)	5 (1.1)	2 (0.4)	1 (0.2)	1 (0.2)	1 (0.2)	3 (0.6)	1 (0.2)	1 (0.2)	0	1 (0.2)	0
Diarrhea	12 (2.5)	2 (0.4)	6 (1.3)	1 (0.2)	0	1 (0.2)	3 (0.6)	2 (0.4)	1 (0.2)	0	0	0

[a]Includes TEAEs in ≥5% in the lumateperone + ADT group and at least twice the rate of placebo + ADT. Included diarrhea due to rounding up to 5%.
[b]N1= the number of patients in the safety population who had treatment duration longer than the start of the time interval. n= the number of patients in the category. Patients with multiple TEAEs are counted only once under the earliest category.
ADT, antidepressant therapy; TEAE, treatment-emergent adverse event.

- The duration of the most common TEAEs is shown in **Table 4**
  - The mean durations for dizziness and somnolence were similar between groups
  - In the lumateperone + ADT group, the mean durations of nausea (7.2 days) and diarrhea (7.3 days) were shorter while the mean durations of fatigue (20.7 days) and dry mouth (22.8 days) were longer than those observed in the placebo + ADT group (nausea: 11.0 days; diarrhea: 12.2 days; fatigue: 11.8 days; dry mouth: 17.3 days)

Table 4. Duration of Common[a] TEAEs During Treatment (Safety Population)

	Lumateperone 42 mg + ADT (n=483)		Placebo + ADT (n=481)	
Preferred Term	Mean (SD), days	Median (range), days	Mean (SD), days	Median (range), days
Dizziness[b]	9.5 (10.85)	5.0 (1-43)	7.7 (8.54)	5.0 (1-31)
Dry mouth	22.8 (12.93)	25.0 (1-43)	17.3 (13.09)	17.0 (1-42)
Somnolence[c]	14.6 (13.09)	9.5 (1-43)	14.9 (13.40)	12.0 (1-44)
Nausea	7.2 (8.25)	5.0 (1-43)	11.0 (12.16)	6.0 (1-39)
Fatigue[d]	20.7 (14.05)	19.0 (2-43)	11.8 (12.15)	6.5 (3-40)
Diarrhea[e]	7.3 (10.42)	2.5 (1-36)	12.2 (11.41)	7.0 (1-31)

[a]Includes TEAEs in ≥5% in the lumateperone + ADT group and at least twice the rate of placebo + ADT. Included diarrhea due to rounding up to 5%. [b]Dizziness includes dizziness and dizziness postural. [c]Somnolence includes hypersomnia, sedation, and somnolence. [d]Fatigue includes asthenia and fatigue. [e]Diarrhea includes diarrhea and frequent bowel movements.
ADT, antidepressant therapy; TEAE, treatment-emergent adverse event

Conclusions

- Lumateperone 42 mg + ADT demonstrated a favorable safety profile in this pooled analysis in patients with MDD with inadequate ADT response
- The majority of TEAEs occurred early in the treatment period, with rates of first onset decreasing throughout the study in the lumateperone + ADT group
- First onset of the most common TEAEs was low (<2%) from Week 2 through the end of treatment
- TEAEs resolved in approximately 1-3 weeks of onset
- These findings support that lumateperone + ADT is generally safe and well tolerated as an adjunctive treatment for patients with MDD with inadequate ADT response

Acknowledgments

The authors thank all study investigators, research staff, and patients for their participation. Medical writing support was provided by Keri Ramessar, PhD, of Nucleus Global, an Inizio company, funded by Intra-Cellular Therapies, a Johnson & Johnson company.

Disclosures

WR Earley, S Durgam, and C Chen are full-time employees of Intra-Cellular Therapies, a Johnson & Johnson company.
SG Kozauer is a former employee of Intra-Cellular Therapies, a Johnson & Johnson company.

AJ Cutler has served as a consultant/on an advisory board for: AbbVie, Acadia, Actinogen, Alfasigma, Alkermes, Anavex Life Sciences, Arrivo BioVentures, Autobahn Therapeutics, Axsome, Biogen, Biohaven, Boehringer Ingelheim, Brii Biosciences, Bristol Myers Squibb, Cerevel, Cognitive Research Corporation, Collegium Pharmaceutical, Corium, Delpor, Evolution Research Group, 4M Therapeutics, Intra-Cellular Therapies, J&J Innovative Medicine, Jazz Pharma, Karuna, Knight Therapeutics, LivoNova, Lundbeck, Luye Pharma, MapLight Therapeutics, MedAvante-ProPhase, Mentavi, Neumora, Neurocrine, Neuroscience Education Institute, NeuroSigma, Noven, Otsuka, PaxMedica, Relmada, Sage Therapeutics, Sirtsei Pharmaceuticals, Supernus, Teva, Thynk, Tris Pharma, Vanda Pharmaceuticals, and VistaGen; Served on a speaker's bureau for: AbbVie, Alfasigma, Alkermes, Axsome, Boehringer Ingelheim, Bristol Myers Squibb, Corium, Intra-Cellular Therapies, Ironshore Pharmaceuticals, J&J, Lundbeck, Neurocrine, Noven, Otsuka, Supernus, Teva, Tris Pharma, and Vanda Pharmaceuticals; Owns stock options/equity with: 4M Therapeutics; Served on a data safety monitoring board for: Alar Pharma, COMPASS Pathways, Freedom Biosciences, and Pain Therapeutics.

SM Stahl has served as a consultant to Acadia, Alkermes, Allergan, AbbVie, Arbor Pharmaceuticals, Axovant, Axsome, Celgene, Concert, Clearview, EMD Serono, Eisai Pharmaceuticals, Ferring, Impel NeuroPharma, Intra-Cellular Therapies Inc., Ironshore Pharmaceuticals, Janssen, Karuna, Lilly, Lundbeck, Merck, Otsuka, Pfizer, Relmada, Sage Therapeutics, Servier, Shire, Sunovion, Takeda, Taliaz, Teva, Tonix, Tris Pharma, and Vifor Pharma; he is a board member of Genomind; he has served on speakers bureaus for Acadia, Lundbeck, Otsuka, Perrigo, Servier, Sunovion, Takeda, Teva, and Vertex; and he has received research and/or grant support from Acadia, Avanir, Braeburn Pharmaceuticals, Lilly, Intra-Cellular Therapies Inc., Ironshore, ISSWSH, Neurocrine, Otsuka, Shire, Sunovion, and TMS NeuroHealth Centers.

Presented at the 64th Annual Meeting of the American College of Neuropsychopharmacology (ACNP), January 12-15, 2026, Nassau, Bahamas

References:

1. Marx W, et al. *Nat Rev Dis Primers*. 2023;9(1):44; 2. Proudman D, et al. *PharmacoEconomics*. 2021;39(6):619-625; 3. Alva G. *CNS Spectr*. 2023;28(5):521-525; 4. Pigott HE, et al. *BMJ Open*. 2023;13(7):e063095; 5. Rafeyan R, et al. *J Clin Psychiatry*. 2020;81(3):OT19037BR3; 6. Titulaer J, et al. *Eur Neuropsychopharmacol*. 2022;62:22-35; 7. Caplyta. Prescribing information. Intra-Cellular Therapies, Inc.;2025; 8. Durgam S, et al. *J Clin Psychiatry*. 2025;86(4):25m15848; 9. Durgam S, et al. *Am J Psychiatry*. 2025;182(12):1072-1082.

Neuropsychiatry

Scan the QR code

The QR code is intended to provide scientific information for individual reference, and the information should not be altered or reproduced in any way.

Email questions to Willie R. Earley at wearley@itci-inc.com